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RESEARCH

N of 1, two contemporary arm, randomised controlled clinical trial for bilateral epicondylitis: a new study design

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Abstract

Objective To investigate the use of a novel study design in analysis of bilateral elbow pain.

Design N of 1, two contemporary arm, open label, randomised controlled clinical trial.

Setting A clinical epidemiologist at a university hospital in Pavia, Italy.

Participants Two elbows with epicondylitis.

Interventions Autologous platelet lysate versus “wait and see” strategy.

Main outcome measures Visual analogue scale for pain on elbow extension and resisted wrist extension.

Results Over six months’ follow-up, the patient experienced bilateral improvement in pain, but higher in the treated arm, with a drop in visual analogue scale for pain from 28 to 4 for right (control) arm (drop of 24 points) and from 67 to 10.5 for left (treated) arm (drop of 56.5 points).

Conclusions Platelet lysate might (or might not) work. Competing interests and lack of blinding might be relevant issues in the interpretation of trial results. However, the new study design can be applied to a number of conditions such as bilateral sport or trauma injuries, bilateral otitis, or any condition affecting chiral organs or limbs.

Introduction

The history of research is replete with examples of researchers experimenting on themselves,[1] but, to our knowledge, this is the first instance where a clinical epidemiologist has drawn up a new study design, performed the trial on herself, and reported the results.

Patient and methods

History

LS, a former infectious disease specialist now a clinical epidemiologist, became the mother of twins in 2007 at the age of 37 years. Two years later, besides representing a quasi-experimental study of the residual effects of chronic sleep loss on human performance[2 3] and of memory impairment by sleep disruption,[4] she had her third relapse of bilateral epicondylitis in less than two years.[5]

After unsuccessful treatments with topical and systemic non-steroidal anti-inflammatory drugs, arm straps, icing, ultrasound therapy, and laser therapy,[6] these episodes were treated with intra-articular corticosteroid injections with high efficacy in the short term.[7] As a result, severe skin atrophy was present bilaterally at the time the study started.

Her blood biochemistry, C reactive protein concentration, erythrocyte sedimentation rate, and tests for rheumatoid factor and autoantibodies were normal. Ultrasound examination revealed bilateral active inflammation and minute intratendinous calcifications. Magnetic resonance imaging confirmed bilateral thickening of the common extensor tendon, with surrounding soft tissue oedema and focal oedema areas in the bone of the radial head and of the lateral epicondyle of the humerus (fig 1⇓).

As symptoms reached Nirschl phase VI to VII, she was about to start a course of antidepressant therapy, when she had a surge of professional pride. Conducting a systematic review of the literature, she found many relevant papers on dozens of possible treatments and focused on a promising report of successful treatment with platelet rich plasma[8] (also expected to reverse

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the deleterious effect of previous steroid injections[9]). She identified an ongoing clinical trial,[10] wrote to the researchers, and was referred to a published abstract indicating 80% success at one year.

Study design

She designed an n of 1, two contemporary arm, open label, randomised controlled trial in which the treatment arm would coincide with the treated arm.[11-14]

For arm A (in the epidemiological sense), treatment with platelet lysate injections (2.5 ml injection every four weeks for three times) was chosen. Platelet lysate is a solution of bioactive molecules obtained by platelet destruction by freeze-thawing.[15]

The choice of the comparator was a challenge. The researcher, having reviewed the literature, found numerous alternatives: acupuncture, shock wave therapy, topical glyceryl trinitrate, transcutaneous electrical nerve stimulation (TENS), tecartherapy, orthotics, physiotherapy, botulinum injections, complete immobilisation, long term arm straps, and surgery.[6] Ultimately, she selected a "wait and see" strategy for the control arm.

Because of the extremely painful nature of the treatment arm (in the epidemiological sense) (local anaesthetics were not allowed, to avoid dilution of the active drug and to limit the injection volume), blinding and masking was not accepted by the patient. In fact, a placebo effect could not be etymologically anticipated, and injection of any amount of inactive liquid into an inextensible and inflamed tendon is likely to be unacceptable.[16]

Randomisation of arms (in the anatomical sense) was deemed appropriate since no residual and differential effect of previous local treatments was hypothesised. Randomisation was achieved by the flipping of a 1 euro coin. No drugs interfering with platelet functions were allowed, nor systemic support in the form of domestic help.

Since the effects on elbows need to be proved,[17] outcome measures for measures were based on a visual analogue scale for pain on elbow extension and resisted wrist extension (primary), on the patient rated tennis elbow evaluation (PRTEE) scale,[18] and other pain and functional scales, and assessed at baseline and at one, three, and six months. All were primary end points to the patient.

Informed consent and other ethical issues

The researchers were not allowed to seek formal ethical committee approval[19] because of an irresolvable conflict of interest (rather a national trait in Italy). Since the patient wished to avoid delays in treatment,[20 21] they did not insist and proceeded with the usual informed consent practices.[22]

Results

Platelet lysate was injected intratendinously by CP on 19 February, 11 March, and 21 April 2010 under sterile conditions (LS, being an infectious disease specialist, particularly stressed the need for hand washing). At the time of first injection (12 months from last corticosteroid injection), skin atrophy had almost completely resolved.

Baseline and follow-up measures are reported in the table⇓ and fig 2⇓. At the one year follow-up, the patient reports having built a piece of furniture by Ikea almost by herself.

Discussion

The relevance of n of 1 trials in evidence based medicine are increasingly recognised.[25] Criteria for determining whether an n of 1 trial is appropriate are well established,[14 26 27] and, according to these, our trial should not have been conducted in view of having to reply "No" to the question "Will the treatment, if effective, be continued long term?"

However, according to the well known principle "There are more things in heaven and earth than are dreamt of in your clinical epidemiology handbook,"[28] we have created a new study design. In this setting, even with cure as the final objective and without repeated periods of treatment, "control-ateral" arm (in the anatomical sense) provides the necessary "control" arm (in the epidemiological sense), thanks to a local treatment being available (that is, with no systemic or controlateral effect anticipated), whereas n of 1 trials have otherwise been used only for systemic treatments.

This new study design could be applied to a number of conditions such as bilateral sport or trauma injuries, bilateral otitis media, bilateral conjunctivitis (indeed, any condition involving chiral organs or limbs).

Study limitations

Many would agree that n of 1 trials do not represent research, but (only) the highest standards of establishing benefits and harms of therapy in an individual.[11 29] On the other hand, as with any single subject research, the generalisability of n of 1 trials is enhanced with within patient (ABA or ABAB designs) replication or between patient replication. This was made explicit by other researchers some years ago—"Death for death, haste still pays haste, and leisure answers leisure; like doth quit like, and measure still for measure."[30] Hopefully, it will not be possible to replicate the trial in this patient. If other patients with bilateral epicondylitis present, other trials will be conducted (we will be glad to provide the research protocol), and results might be combined.[31]

A considerable source of bias is the fact that the patient is a researcher as well. Single self experiments have been categorised as self indulgence or abuse, and trivial interventions masquerading as research studies as a source of amusement.[19] In the present study, the intervention was by no means trivial, requiring high scientific, clinical, and technical expertise from the investigators, and high motivation from the patient. Besides, experimental units were two (right and left elbows), and the patient-researcher was at the same time self indulgent (right elbow) and self abusing (left elbow). Finally, she was in no way amused by the clinical situation.

In addition, the patient was not blind to the treated arm, and objective measures were not used. However, the patient was carefully instructed to forget which arm was given which treatment, was sent electronic reminders of the scheduled assessments to avoid missing data, and, in case she forgot despite all this,[4] the researcher filled in the questionnaires herself.

Conclusions

At end of the trial, both arms were almost pain-free, but the drop in pain in the treated arm was greater than in the control arm. This allows several different conclusions to be drawn on efficacy of platelet lysate in chronic refractory epicondylitis:

1) It is effective, since drop in pain was steeper in the treated arm

2) It is not effective, and improvement was due to the natural course of lateral epicondylitis

3) It is effective, and the parallel improvement in the untreated arm could have been mediated by the improvement in the treated arm, by allowing a more equal distribution of workload

4) Both arms benefited from participation into a clinical trial[32]

5) More studies are needed.

Contributors: LS drafted the study protocol, submitted (unsuccessfully) the study protocol to the ethics committee, underwent the experimental treatment, collected the data, performed the statistical analyses, and drafted the report. She is the guarantor. CDF drew blood from LS, prepared the lysate and, more importantly, held the patient's hand during the injections. CP participated in drafting the study protocol and preparation of lysate injections. CFP performed the injections (without anaesthesia, a reason why his authorship should not be allowed). DC performed radiological examinations. VS led the systematic review of the literature and retrieved even the most improbable reports from the most elusive medical and lay journals. CT had the original idea for the study, supervised data collection and clinical assessments, checked data quality control, and performed the randomisation.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) LS is the patient-researcher, (2) all the others are her friends and colleagues and all have personal interests relevant to the present work since they were definitely fed up with LS's complaints about her pain and disability related scores in QoL questionnaires, (3) no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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What is already known on this topic

Single self experiments are common in all fields of medicine except clinical epidemiology

There are more things in heaven and earth than are dreamt of in your clinical epidemiology handbook

What this study adds

An example of self experimentation in clinical epidemiology

A novel study design

Not much else

Table

Table 1| Baseline and follow-up measures of elbow pain and function in control (right) and treated (left) arms

	Right arm	Left arm	Difference left–right
Baseline:			
VAS score*	28	67	39
PRTEE scale†	31.5	48.5	17
Mayo score‡	52.5	30	−22.5
Roles-Maudsley score§	4	4	0
1 month follow-up:			
VAS score*	25	65	40
PRTEE scale†	28.5	42.5	14
Mayo score‡	57.5	35	−22.5
Roles-Maudsley score§	3	4	1
3 month follow-up:			
VAS score*	13	34	21
PRTEE scale†	11.5	19.5	8
Mayo score‡	82.5	77.5	−5
Roles-Maudsley score§	1	2	1
6 month follow-up:			
VAS score*	4	10.5	6.5
PRTEE scale†	5	10.5	5.5
Mayo score‡	87.5	80	−7.5
Roles-Maudsley score§	1	2	1
Difference 6 months−baseline:			
VAS score*	−24	−56.5	−32.5
PRTEE scale†	−26.5	−38	−11.5
Mayo score‡	35	50	15
Roles-Maudsley score§	−3	−2	1

*VAS=visual analogue scale, median value of twice daily measurements over 7 days (n=14).

†PRTEE=patient rated tennis elbow evaluation scale.[18]

‡Mayo functional elbow score.[23]

§Roles-Maudsley score.[24]

Figures

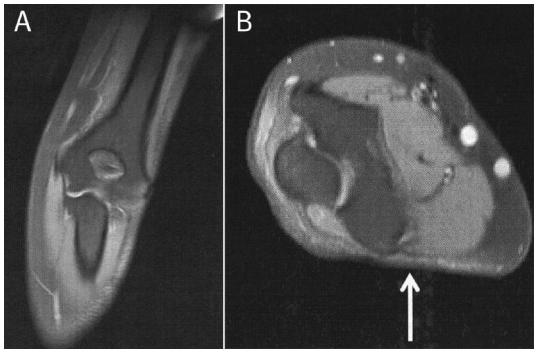

Fig 1 Magnetic resonance imaging (turbo spin echo, fat saturated, proton density weighted) of the patient's left elbow in coronal (A) and transverse (B) views. Images show signal hyperintensity in the medial epicondyle and lateral osteophytes of the olecranon, and severe skin atrophy (arrow). (Translation into English: it is very painful)

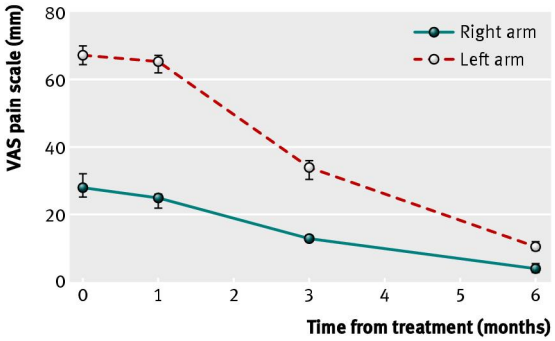

Fig 2 Median (interquartile range) measures of elbow pain on visual analogue scale (VAS) for the right (control) and left (treated) arms in the first six months from treatment